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More Genes for Thoracic Aortic Aneurysms and Dissections

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2013 (5) suggest that many clinicians, including noncardiovascular specialists, will encounter a patient on, or will themselves prescribe, an oral anticoagulant. Clinicians should familiarize themselves with these effective yet potentially harmful agents.

Despite their greater cost, DOACs may soon overtake warfarin as the predominant oral anticoagulant prescribed to Medicaid beneficiaries. Due to the structure of the American health care system, the actual out-of-pocket expense to a patient varies widely and represents a fraction of the drug's wholesale price. Although warfarin copays are likely less expensive than DOAC copays, this difference does not appear to preclude DOAC use. Moreover, we speculate that rivaroxaban's once-daily administration and apixaban's favorable safety profile drive clinician preferences for these DOACs. Relative underuse of dabigatran may be attributable to its gastrointestinal intolerance, whereas edoxaban's underuse may be due to its unusual dosing (contraindicated if creatinine clearance >95 ml/min in atrial fibrillation) and being last to market.

This analysis lacked patient-level and cost data. Thus, we could not differentiate between new and existing users of oral anticoagulants or the characteristics of such persons. Nevertheless, oral anticoagulant use, primarily due to DOAC use, is increasing among Medicaid beneficiaries.

In conclusion, we found that DOACs have begun to displace warfarin as the predominantly used oral anticoagulant among patients with limited financial resources despite the higher overall cost of these agents.

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More Genes for Thoracic Aortic Aneurysms and Dissections

In the current genomics era, technological advances have led to the identification of an increasing number of gene-disease associations. In a recent issue of the *Journal*, Renard et al. (1) assessed and clinically validated genes that may predispose to syndromic or nonsyndromic forms of heritable thoracic aortic aneurysm and dissection (HTAAD), classifying a total of 53 genes into 5 categories (from "definitive/strong" to "no evidence"). Such expert-curated gene categories and panels, which need to be updated regularly, facilitate the challenging interpretation of sequence variants detected by high-throughput clinical sequencing (2). To update the study of Renard et al. (1), we propose to extend the category "recent genes" by *AEBP1*, *LMOD1*, and *LTBP3* (**Table 1**), because heterozygous (*LMOD1*) or biallelic (*AEBP1* and *LTBP3*) pathogenic sequence variants in these genes have very recently been reported in aortic aneurysm cases with syndromic or nonsyndromic presentations (3–5). Furthermore, we propose to include additional genes, which are, like these 3 recent and many of the 53 curated genes, highly expressed in the aorta but lowly expressed in other tissues (the Genotype-Tissue Expression [GTEx] project), in particular *EFEMP1*, *LTBP1*, and *MFAP4* (**Table 1**), into category D ("no evidence") for research-based mutation screening in unsolved HTAAD cases. Moreover, in addition to the clinical validity of genes and the type/location of sequence variants, we propose to consider other, less widely known, challenges/pitfalls in the clinical interpretation of pathogenicity (2), including random autosomal monoallelic expression and the GTEx-based clarification whether or not the isoforms expressed in the aorta are indeed affected (**Table 1**).

TABLE 1 Additional Genes for HTAAD

HGNC Gene Symbol (Protein Coding Isoform Highly Expressed in the Aorta*)	Gene Function	Median Expression, TPM*		Reason for Listing	Aortic Disease Risk as Reported in the Published Data (Ref. #)	Inferred Expression (Tissue)†
		Aorta	Fibroblasts			
Genes proposed for the category "recent genes"						
AEBP1 (ENST00000223357, ENST00000450684)	VSMC differentiation	2,285	118	Recent publication, highly expressed in the aorta	1 publication reporting 1 proband with TAA requiring surgery (4)	Biallelic (HUVEC)
LMOD1 (ENST00000367288)	VSMC contraction	1,114	11	Recent publication, highly expressed in the aorta	1 publication reporting >6 probands with TAA/AD (3)	Undetermined (HUVEC)
LTBP3 (ENST00000322147)	TGF-β sequestration	372	78	Recent publication, highly expressed in the aorta	1 publication reporting 7 probands with TAA/AD (5)	Biallelic (HUVEC)
Genes proposed for the category D ("no evidence")						
EFEMP1 (ENST00000355426, ENST00000394555)	ECM component, MMP regulation, VSMC homeostasis	1,332	451	Gene function, highly expressed in the aorta	No probands with TAA/AD found	Biallelic (HUVEC)
LTBP1 (ENST00000404525, ENST00000418533)	TGF-β sequestration	565	229	Gene function, highly expressed in the aorta	No probands with TAA/AD found	Biallelic (HUVEC)
MFAP4 (ENST00000299610)	ECM component	1,757	198	Gene function, highly expressed in the aorta	No probands with TAA/AD found	Monoallelic (murine heart; no data in human tissue)

*According to the Genotype-Tissue Expression (GTEx) project. †According to dbMAE: the database of autosomal monoallelic expression.

AD = aortic dissection; ECM = extracellular matrix; HTAAD = Heritable Thoracic Aortic Aneurysms and Dissections; HUVEC = human vascular epithelium cell lines; MMP = matrix metalloproteinase; TAA = thoracic aortic aneurysm; TGF-β = transforming growth factor β; TPM = transcripts per million; VSMC = vascular smooth muscle cell.

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REPLY: More Genes for Thoracic Aortic Aneurysms and Dissections

We appreciate the valid comments by Caspar and colleagues on our recent paper entitled "Clinical Validity of Genes for Heritable Thoracic Aortic Aneurysms and Dissections" (1). Fifty-three potential heritable thoracic aortic aneurysm and dissection (HTAAD) genes were curated using a semiquantitative method developed by ClinGen (2), resulting in 5 categories, depending on the strength of the gene-disease relationship, ranging from "definitive" to "no evidence."

Caspar and colleagues suggest adding 3 genes that were published after our manuscript was submitted. We agree that these need to be curated. This comment reflects our discussion point that regular and easily accessible updates of these published data are required. ClinGen is currently working on a strategy to implement regular updates of gene-disease curations.

Applying the gene-disease curation matrix reveals the following results: